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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,189	01/16/2002	Berish Rubin	Rubin-201-KGB	6280

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,189	RUBIN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *9-12* is/are withdrawn from consideration.

5)☒ Claim(s) *8 and 13* is/are allowed.

6)☒ Claim(s) *1-7 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/21/03, 1/16/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-8 and 14-17 in the reply filed on September 20, 2004 is acknowledged. Claim 13 has been rejoined with the subject matter of Group I. Accordingly, claims 1-8 and 13-17 have been examined herein.

The traversal is on the ground(s) that restriction is only required when the inventions are independent and distinct. This is not found persuasive because dependent inventions may be properly restricted if they are distinct. As discussed in MPEP 803, one of the two criteria for requirement of restriction is that the "inventions must be independent (see MPEP 802.01, 806.04, 808.01) or distinct as claimed". Accordingly, the demonstration of distinctness of the inventions is sufficient grounds for restriction. As stated in MPEP 802.01 "(t)he law has long been established that dependent inventions (frequently termed related inventions) such as those used for illustration above may be properly divided if they are, in fact "distinct" inventions, even though dependent". Applicants further argue that the classification of an invention is an unreliable basis for requiring restriction. However, classification of an invention does establish the context of the invention and exemplifies the diversity of the subject matter claimed and thereby is a criteria to be considered when determining the appropriateness of a restriction requirement. Further, the restriction requirement was not based solely on the different classification of the inventions, but on the fact that, as stated above, the inventions are in fact distinct and a search for the subject matter of invention I is not co-extensive with a search of invention II. For example, a search for

references teaching a method of detecting the presence of a mutation in the IKAP gene is not co-extensive with a search for references teaching mutated IKAP genes, since such genes may be disclosed in references without the references disclosing the presence of a mutation or a method for detecting a mutation. Accordingly, undue burden would be required to examine the subject matter of Group II together with the subject matter of Group I.

The requirement is still deemed proper and is therefore made FINAL.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

In particular, the first line of the specification should be amended to indicate that the present application claims priority under 35 U.S. C. 119(e) to provisional application 60/262,284, filed January 17, 2001.

Objections

3. Claims 14-17 are objected to because of the following informalities:

In claims 14-17, "isolated of RNA" should read "isolating RNA" (see line 2 of claim 14).

Claim Rejections - 35 USC § 112

4. Claims 1, 2, and 14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for detecting the presence of a T to C at position 6 of the donor splice site of intron 20 of the gene encoding the IkappaB kinase-complex associated protein (IKAP) and methods for detecting the presence of a G to C transversion of nucleotide 2390 in exon 19 of the IKAP gene, which results in an arginine to proline substitution at amino acid residue 696 of IKAP, does not reasonably provide enablement for methods which detect any disruptive mutation in the IKAP gene or methods which detect the T to C splice mutation in intron 20 or the G to C transversion in exon 19 of any gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1 and 2 are drawn broadly to encompass methods which detect any disruptive mutation in the IKAP gene. The claims do not define the location or identity of the mutation. Claims 14-17 are drawn to methods which detect a T to C splice mutation in intron 20 or the G to C transversion in exon 19 of any gene. That is, claims 14-17 do not specify any particular gene which contains the stated mutations.

Nature of the Invention and State of the Art:

The specification (see, e.g. page 3) teaches 2 mutations in the IKAP gene: a) a first mutation located at bp 6 within intron 20, wherein a thymine is replaced by a cytosine (i.e. "2507+6T"); and b) a second mutation at position 2390 of GenBAnk Accession No. NM_003640, which results in a substitution of arginine to proline at amino acid position 696. The art teaches the complete cDNA sequence and genomic sequence of the IKAP gene. In particular, Slaugenhaupt (US 2002/0169299) teaches that the IKAP genomic DNA spans 66,479 nucleotides. The specification and prior art do not teach any additional mutations in the IKAP gene and particularly does not teach any additional IKAP mutations associated with FD. Further, the prior art does not appear to teach any additional genes which are associated with FD or any additional mutations which are associated with FD.

The Relative Skill in the Art:

The level of skill in the art of molecular biology and diagnostics is relatively high.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying genes associated with a disease and detecting the presence of novel mutations associated with the occurrence of disease is highly

unpredictable. Knowledge of the 2507+6T and R696P mutations does not lead one to any additional mutations in the IKAP gene or to the presence of these mutations in any other gene. There is no common structural feature linking the broadly claimed mutations. It is noted the specification does not specifically define what is intended to be encompassed by a "disruptive mutation." Accordingly, such mutations are considered to include polymorphisms in regulatory, intron and coding sequences which do not alter the coding sequence or expression levels, but which nonetheless are still associated with FD. With respect to the IKAP gene, it is unpredictable as to which residues within this gene of over 60Kb are important to the functional activity of the encoded protein or the expression of the protein and which nucleotides are variable in nature and are associated with the occurrence of FD. To identify additional genes or mutations associated with FD requires extensive, trial-by-error experimentation in which researchers may be required to map genes, perform linkage analysis to determine the inheritance pattern of polymorphisms, sequence genes, identify specific mutations in the sequenced gene, analyze members of the population which have FD and individuals who do not have FD for the presence or absence of a polymorphism or mutation and try to ascertain which specific polymorphisms or mutations are associated with the occurrence of disease. Such experimentation is considered to be undue.

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably identify additional mutations in the IKAP gene or as to how to identify additional genes containing the 2507+6T and R696P mutations. While methods for sequencing genes

and comparing the sequence of genes from patients and control individuals are known in the art, such methods provide only the general guidelines that allow researchers to search for novel mutations. Providing methods for searching for a mutation and for additional FD-associated genes is not equivalent to teaching how to make and use specific mutations that are associated with FD.

Working Examples:

Again, the specification (pages 3, 9 and 10) teaches 2 mutations in the IKAP gene, namely the 2507+6T and R696P mutations. The specification does not provide any additional examples of FD-associated mutations in the IKAP gene or in other unspecified genes.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the claims do not bear a

reasonable correlation to the scope of enablement because the specification teaches only 2 members of the broadly claimed genus of disruptive mutations associated with FD. As set forth above, in view of the unpredictability in the art, extensive experimentation would be required to identify additional IKAP mutations and mutations in other genes associated with FD. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art as to additional polymorphisms or mutations which are associated with FD and the lack of specific guidance provided by the specification, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 and 14-17 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are indefinite. The claims are drawn to a method for detecting the presence of a polymorphism linked to a gene associated with FD, but recite only a step of detecting a disruptive mutation in the IKAP gene. The claims do not clarify the relationship between the polymorphism linked to a gene associated with FD and the disruptive mutation in the IKAP gene and thereby the claims do not recite a clear nexus between the preamble of the claim and the method steps of the claim. Further, it is

unclear as to whether the polymorphism is considered to be the same as or different from the mutation.

Claims 4-6 are indefinite over the recitation of "nucleotide 2390 in exon 19" because the claims do not provide a clear context for determining the location of this mutation. The numbering of the IKAP cDNA varies in the prior art due to the presence of 2 distinct IKAP mRNA transcripts (see, e.g., Slaughenhaupt, page 10, column 2). The claims do not clearly set forth a reference point that would allow for the unambiguous identification of the stated mutation. Accordingly, one cannot determine the meets and bounds of the claimed invention.

Claims 14-17 are indefinite and vague because the claims recite the location of a mutation, i.e., position 6 of the donor splice site of intron 20 and position 2390 in exon 19, but do not recite the identity of the gene containing these mutations. Thereby, the claims do not clearly set forth a reference point that would allow for the unambiguous identification of the stated mutations. Accordingly, one cannot determine the meets and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-6 and 14-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Slaugenhaupt (US 2002/0169299; cited in the IDS).

Slaugenhaupt (pages 10-12) teaches methods for detecting the presence of a mutation in the IKAP gene (referred to therein as the "IKBKAP" gene). In particular, Slaugenhaupt teaches methods which detect the presence of the T to C substitution at position 6 in the donor splice site of intron 20 and methods which detect the presence of a G to C transversion in exon 19, which results in an arginine to proline substitution at amino acid position 696 (referred to therein as nucleotide position 2397; see page 1, column 2). Slaugenhaupt teaches that the presence of each of these mutations is associated with the occurrence of FD (page 11). With respect to claims 5 and 6, Slaugenhaupt teaches that the nucleic acid to be analyzed is obtained by PCR amplification (page 4, column 2) and that the mutation may be detected by SSCP analysis (page 5, column 2). Accordingly, the method of Slaugenhaupt anticipates the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Carla Myers
December 8, 2004

CARLA J. MYERS
PRIMARY EXAMINER